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Dedicated to the 115th anniversary of B.A. Arbuzov's birth

Spatial Structure of Tetrasubstituted Thiacalix[4]arenes Containing L-Tryptophan Fragments in Solution

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Abstract—The steric structure of the *cone* and *1,3-alternate* stereoisomers of *p-tert*-butylthiacalix[4]arenes bearing in the lower rim four substituents containing amide and ammonium groups as well as L-tryptophan residues was studied by ^{1}H, ^{13}C, $^{1}H–^{1}H$ NOESY, and $^{1}H–^{13}C$ HSQC NMR spectroscopy. The mutual repulsion of the charged ammonium groups and the presence of intramolecular hydrogen bonds in the synthesized compounds can make the peptide bond with the tryptophan residue sterically accessible for enzymes.

Keywords: thiacalix[4]arene, ammonium salts, tryptophan, NMR spectroscopy, macrocycles

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Knowledge of the 3D structure of proteins is necessary for understanding at molecular level of vital biochemical processes in animal and human bodies [1]. However, the study of such processes *in vivo* is quite difficult and complicated by a variety of interfering factors. Therefore, over the past years, a lot of synthetic supramolecular systems for mimicking the functions of complex biological objects have been designed in the framework of the biomimetic approach [1]. Such artificial abiotic molecular structures or reactions are used as models to gain insight into the corresponding regularities. The use of low-molecular-weight water-soluble polyfunctional compounds is a successful approach to the design of such models. The thiacalix[4] arene scaffold is among convenient and popular macrocyclic structures. The design of water-soluble thiacalix[4]arene derivatives containing amino acid residues in the lower rim is a nontrivial task in macrocyclic chemistry.

It is well known that the spatial arrangement of substituents with respect both to the macroring and to each other determines the physical (melting point) and chemical (complex formation, association, etc.) properties of thiacalixarenes. Moreover, the structures containing a peptide bond with the N-terminal fragment of the L-tryptophan residues have found application as digestive enzyme modulators [2]. In this connection research into the steric structure of quaternary ammonium salts derived from *p-tert*-butylthiacalix[4] arenes containing the L-tryptophan residues in the lower rim is of immediate interest.

The diversity of macrocyclic platforms (calixarenes, calixresorcinolarenes, calixpyrroles, pillararenes, calixpyrogallols, cyclodextrins) opens up unlimited perspectives for varying the structure of compounds of these classes, which exhibit amphiphilic properties and are capable of binding organic and inorganic cations and anions and are self-assembling in aqueous and organic media [3–15]. The solubility of the synthesized macrocycles in water can be increased by introducing in their structures different charged fragments like carboxylate, sulfonate, guanidine, and ammonium [16–19].

In the present work we focused on fairly readily accessible ammonium derivatives of thiacalix[4]arene. By combining the nontoxic thiacalixarene macrocyclic scaffold with biologically active ammonium derivatives we expected to obtain water-soluble compounds capable of self-assembling. The modification of the macrocyclic scaffold with natural amino acid residues would increase the affinity of the synthesized compounds to macromolecular biological objects like nucleic acids and proteins.